B3 11. (Amended) The DNA [sequence] construct of claim 1 wherein said protein is human tissue plasminogen activator or hepatitis B surface antigen.

REMARKS

Claims 1, 2, 4-9 and 11 are amended to more clearly recite and distinctly claim subject matter which Applicants believe to be their invention. No new subject matter has been added. Upon entry of this amendment, claims 1, 2, 4-9 and 11 are in the case, and claim 3 is canceled without prejudice.

Applicants gratefully acknowledge the interview granted on June 16, 1993 between Examiner Chambers and the undersigned. The outstanding rejections, along with the enclosed declarations under 37 CFR 1.132 were discussed at the interview. Applicants have amended the pending claims and present two declarations under 37 C.F.R. §1.132 in accordance with discussions which occurred between Examiner Chambers and the undersigned during said interview. The Declarant on both rule 132 declarations is Dr. Katherine Gordon, a co-inventor of the presently claimed DNA constructs. As discussed at the June 16th interview, a first declaration swears as to the details of a DNA construct, as claimed, and its use in generating a transgenic animal producing a recombinant protein in its milk. A second declaration sets forth evidence that one of ordinary skill in the art would have reasonably expected transcription regulatory sequences of other members of the class of milk serum proteins to function in the same or similar manner as the illustrative WAP construct. The above amendments and declarations are believed to resolve all remaining section 112 issues and place the claims in condition for allowance.

Rejection Under 35 USC 112, first paragraph

Claims 1-3, 5-9 and 11 were "rejected under 35 USC 112, first paragraph, as the disclosure is enabling only for claims limited to a DNA sequence comprising a whey acidic

protein promoter". Particularly, the Examiner states that "[t]he specification is not enabling for a DNA sequence comprising all milk serum promoters" and that "the specification only discloses the construction of fusion genes using a single milk protein promoter". It is the Examiner's position that "it is well known in the art that the level and mode of expression of each transgene as well as the effects of its expression on the animal as a whole are not readily predictable due to uncontrollable factors such as the site of integration of the transgene".

The above rejection is respectfully traversed. One of ordinary skill in the art at the time the invention was made would have reasonably expected milk protein promoters, e.g. milk serum protein promoters, to function within the claimed invention in the same or similar manner absent evidence to the contrary. At the time the claimed invention was made, it was reasonable to expect milk proteins to share similar regulatory mechanisms and regulatory sequences. It is further submitted that the Examiner has not fulfilled her burden of providing a reason why one of ordinary skill in the art would not have reasonably expected other milk serum promoters to function within the presently claimed invention. A broad statement that "the mode of expression of each transgene as well as the effects of its expression on the animal as a whole are not readily predictable" does not fulfill her burden. Applicants were not claiming all "transgenes" but rather were claiming a specific set of transgenes (transgenes containing a milk protein promoter). It is respectfully requested that the Examiner provide a specific reason why one of ordinary skill in the art would not expect the claimed DNA constructs to function within the present invention if the above rejection is maintained.

It is even further submitted that the above rejection does not pertain to the claims as newly amended. The newly amended claims are drawn to DNA constructs containing a gene being under transcriptional control of a mammalian milk serum protein promoter which is the class of promoters of which the WAP promoter is a member. The Gordon Declaration filed concurrently herewith under 37 C.F.R. 1.132 (hereinafter Gordon Declaration) supports Applicants' position that one of ordinary skill in the art would have reasonably expected that

transcriptional regulatory sequences derived from other members of the class of milk serum proteins would function within the claimed DNA constructs in the same or similar manner as the WAP regulatory sequences (see page four of the Gordon Declaration).

Rejections Under 35 USC 103

Applicants respectfully contend that the subject matter of the pending claims is patentably distinct from the art of record. Fundamentally, the Applicants' claims are directed to DNA sequences encoding recombinant proteins for secretion into the milk of transgenic animals. The DNA construct comprises a gene encoding a protein, the gene being under transcriptional control of a promoter of a milk serum protein gene. The DNA construct also includes DNA encoding a peptide which enables secretion of the protein.

The cited Andres et al. reference contains no facts that teach or suggest the presently claimed DNA constructs, particularly a DNA construct which encodes a recombinant protein and further includes a DNA sequence encoding a peptide which provides a means for secretion of that protein. Andres et al. merely disclose a genetic construct comprising a human Ha-ras gene under the control of a promoter region of the WAP gene. As the outstanding Office Action concedes at page 3, paragraph 5, the Andres et al. reference lacks any teaching that a secretion signal sequence be added to the construct to facilitate secretion of Ha-ras, let alone to direct secretion of therapeutically active protein. To arrive at such a combination, the Examiner argues that

> "it would have been obvious for one of ordinary skill in the art to modify the DNA construct taught by Andres et al. by inserting into the construct the whey acidic protein signal sequence for the *expected benefit* of obtaining secretion of the human H-ras protein into milk..." [emphasis added].

However, Applicants contend that construing the Andres et al. teachings in such a manner is without merit, as the reference lacks any motivation to produce a secreted form of the ras protein.

The goal of Andres et al. in expressing the ras oncogene in mammary epithelial cells of transgenic mice was to study the effect of a specific oncogene on this particular cell type *in vivo*. To elucidate the effects of a specific oncogenic protein on particular specialized cell types, it is desirable to restrict the expression of that oncogene to a limited subset of cells and possibly to restrict its expression. Targeting of gene expression in transgenic animals by recombination of an oncogene with differentiated cell-type specific gene promoters provides an ideal system for analyzing the effect of an oncogene on a particular cell type *in vivo*. Andres et al. directed expression of the activated Ha-ras gene to the lactating mammary epithelial cells with a fragment from the murine WAP gene containing mammary specific promoter sequences. As it is only active during lactation, the WAP fragment conferred the hormone dependence to the ras expression. Under the hormonal stimulus, the expression of the chimeric gene was therefore predominantly restricted to the mammary gland and the effect of ras on that tissue can be determined.

any protein

Applicants contend that modifying Andres et al. to provide for the secretion of ras would be counter to the teaching of that reference. The oncogenic properties of ras are derived from the its presence within the cell, not extracellularly. Thus, there would be no *expected benefit* as argued by the Examiner, and therefore no motivation, to adding the WAP secretion signal sequences to the ras hybrid gene of Andres et al.

- obvious modif.

Turning to the rejection of the pending claims under 35 U.S.C. 103 as being unpatentable over the combination of Campbell et al., Pennica et al., Chisari et al., Palmiter et al., Ross et al., and Stewart et al., Applicants assert that the mere fact that the prior art could be modified to produce the claimed DNA constructs does not make the modifications obvious unless the prior art suggested the desirability of the modification.

Campbell et al. disclose the characterization of genomic clones of the mouse and rat WAP genes. In particular, Campbell et al. investigated the 5' and 3' non-coding sequences which flank the coding sequence of the protein, and identified several potential regulatory sequences of

the WAP gene which may be related to the regulation of WAP expression. However, as the outstanding Office Action admits at page 4, paragraph four, in contrast to the pending claims, the Campbell et al. reference does ***not*** teach a DNA construct comprising a gene encoding a recombinant protein and under the transcriptional control of a mammalian milk serum protein, let alone that the DNA construct also provides, upon expression, a peptide which enables secretion of the recombinant protein. Applicants allege that Campbell et al. fails to teach or suggest the desirability of the claimed construct, and thus would not itself have rendered the subject matter of the pending claims obvious.

Applicants further contend that the secondary art of record, whether taken individually or in combination, *fails* to bridge the gap between Campbell et al. and the claimed DNA constructs. While Pennica et al. disclose DNA constructs for expressing tPA in *E. coli*, they in no way appreciate that transcriptional regulatory sequences of a milk serum protein, such as WAP, could be used to drive production of tPA (or any recombinant protein) in milk. In fact, Pennica et al. turned to prokaryotic expression systems, rather than eukaryotic expression systems, in order to produce recombinant tPA, and therefore do not supply the necessary suggestion to modify Campbell et al.

Likewise, Chisari et al. fail to propose the desirability of the Examiner's suggested modification. The transgenic mouse generated by Chisari et al. was an attempt to establish a model analogous to the stage in hepatitis B virus (HBV) infection when replication has ceased and the viral DNA has integrated into the host genome, as occurs in the chronic carrier state and in hepatocellular carcinoma. As set forth at page 60 in the paragraph bridging columns one and two, such models were intended to provide an opportunity to study the consequences of expression of integrated HBV DNA in genetically defined mice of predetermined immune responsiveness, and provide useful information pertaining to the pathogenesis of the disease in man. To modify the expression of the HBV antigens so as to place them under the particular control of milk serum protein regulatory elements and direct their expression to milk would be

contrary to the express goals Chisari et al., and such a suggestion is neither explicit in, nor fairly inferred from the reference.

The Palmiter et al. reference has been cited by the Examiner as disclosing, in the manner of a review article, different studies on the tissue-specific expression of recombinant gene products in transgenic animals. However, Applicants submit that Palmiter et al. provides no teaching, suggestion, or incentive to combine the Campbell et al. reference with either of the Chisari et al. or Pennica et al. references. With regard to tissue-specific expression of recombinant proteins in lactating mammary epithelia, Palmiter et al. go no further than Andres et al. (supra) or Stewart et al. (infra) in that Palmiter et al. merely disclose the use of transgenic animals to probe the effect of particular oncogenes on that tissue, and thus does not discuss or infer the production of recombinant proteins in milk of transgenic animals.

Each of the Ross et al. and Stewart et al. references disclose the use of the mouse mammary tumor virus (MTV) promoter, *not* milk protein gene regulatory sequences, to drive tissue specific expression of recombinant proteins in the mammary glands of transgenic mice. Moreover, neither reference contains any facts that teach or suggest that Campbell et al. be modified with the coding sequences of tPA, HBsAg, or any other recombinant protein to be secreted into the milk of a transgenic animal.

As with the Andres et al. reference discussed above, Stewart et al. sought to assess the effect that an oncogene, in this instance the myc oncogene, might have on the normal process of development in a living organism. As described above, the teachings of such a reference are incompatible with the production of a recombinant protein in the milk of a transgenic animal.

In the instance of Ross et al., the goal was to assess whether the tissue-specific expression of MTV, as well as the functional response to the glucocorticoid receptor binding sites, was due to MTV-encoded sequences or to chromosomal position of the endogenous provirus. See Ross et al. at page 5880, column one, third paragraph. Ross et al. generated chimeric mice with a DNA construct comprising the MTV long terminal repeat and a thymidine kinase (TK) gene.

Applicants note that TK, like the oncogenes of Andres et al. and Stewart et al., is a protein localized within a cell and not actively secreted. In fact, Ross et al. were not even concerned with the production of the protein per se, rather, they only scored for the presence of integration of the construct and the level of mRNA produced by the construct.

The fact remains that prior to the Applicants' invention, no one had produced transgenic animals which secreted recombinant proteins in their milk using the claimed DNA constructs. The claimed DNA construct serves a purpose, and has properties, that are not disclosed or suggested in the prior art. Applicants emphasize that obviousness cannot be established by combining the teaching of the prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. As set out above, none of the cited references disclose the presently claimed DNA constructs, particularly a DNA construct which encodes a recombinant protein and further includes a DNA sequence encoding a peptide which provides a means for secretion of that protein as is set forth in amended claim 1.

Summary

It is respectfully submitted that the above rejections are improper and/or do not pertain to the claims as newly amended and should be withdrawn. Any amendments made to the claims should not be construed as acquiescences to the Examiner's rejections and are being made to expedite prosecution of the above-identified application. Applicants reserve the right to file broader claims (including the originally filed claims) in related applications.

If a telephone conversation with Applicants' Attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at the telephone number listed below.

Respectfully submitted,

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